

## REMARKS

Claims 1-14 and 29-40 are pending in this application. It is respectfully requested that this application be amended by amending claims 1, 2, 14, 29, 32, 36, 39 and 40 and adding claims 41-45.

Claim 1 has been amended to correct -N(C(O)CF<sub>3</sub>).

Claim 2 has been amended to correct the case of SO<sub>2</sub>(C<sub>1</sub>-C<sub>6</sub> alkyl).

Claim 12 has been amended to add "4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine - (disclosed on page 11, line 2 of the specification); [3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine - (disclosed on page 10, line 32 of the specification) and [2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine - (disclosed on page 16, line 11 of the specification).

Claim 13 has been amended to delete the phrases "such as fibromyalgia" and "including cerebral ischemia" and to add "excitotoxic neuronal damage." Support for the addition of "excitotoxic neuronal damage" in claim 13 is found on page 24, line 27 of the specification.

New claim 41 depends from claim 13 and defines the pain perception as fibromyalgia.

New claim 42 depends from claim 13 and defines the ischemic neuronal damage as cerebral ischemia.

Claim 14 has been amended to delete the phrase "such as depression and postpartum depression" and delete ", including a human".

New claim 43 depends from claim 14 and defines the mood disorders as depression or postpartum depression.

New claim 44 depends from claim 14 and defines the ischemic neuronal damage as cerebral ischemia.

New claim 45 depends from claim 14 and defines a mammal as a human.

Claim 29 has been amended to replace "R24 and R25" with "R<sub>24</sub> and R<sub>25</sub>".

Claim 36 has been amended to delete the word "including" in line 2 of the claim.

Claim 39 has been amended to depend from claim 44 and to delete "excitotoxic

neuronal damage” which has been added to claim 13.

Claim 40 has been amended to place a period at the end of the claim.

In view of these amendments, it is respectfully requested that the objections to claims 2, 13, 14, and 29 and the rejection of claims 1-14 and 29-40 under 35 USC 112, second paragraph be withdrawn.

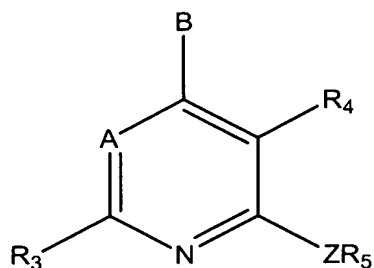
Respectfully submitted,

A handwritten signature in black ink, appearing to read "Janet I. Cord", with a long horizontal flourish extending to the right.

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Claim 1 (Twice Amended). A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is N;

B is  $-\text{NR}_1\text{R}_2$ ,  $-\text{CR}_1\text{R}_2\text{R}_{11}$ ,  $-\text{C}(=\text{CR}_2\text{R}_{12})\text{R}_1$ ,  $-\text{NHCHR}_1\text{R}_2$ ,  $-\text{OCHR}_1\text{R}_2$ ,  $-\text{SCHR}_1\text{R}_2$ ,  $-\text{CHR}_2\text{OR}_1$ ,  $-\text{CHR}_1\text{OR}_2$ ,  $-\text{CHR}_2\text{SR}_1$ ,  $-\text{C}(\text{S})\text{R}_2$ ,  $-\text{C}(\text{O})\text{R}_2$ ,  $-\text{CHR}_2\text{NR}_1\text{R}[2]_2$ ,  $-\text{CHR}_1\text{NHR}_2$ ,  $-\text{CHR}_1\text{N}(\text{CH}_3)\text{R}_2$ , or  $-\text{NR}_{12}\text{NR}_1\text{R}_2$ ;

Z is NH, O, S,  $-\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})-$ ,  $[-\text{NC}(\text{O})\text{CF}_3]$ ,  $\text{N}(\text{C}(\text{O})\text{CF}_3)_2$ , or  $-\text{C}(\text{R}_{13}\text{R}_{14})-$ , wherein  $\text{R}_{13}$  and  $\text{R}_{14}$  are each, independently, hydrogen, trifluoromethyl or methyl, or one of  $\text{R}_{13}$  and  $\text{R}_{14}$  is cyano and the other is hydrogen or methyl, or  $-\text{C}(\text{R}_{13}\text{R}_{14})$  is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with  $\text{R}_5$ , which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen,  $\text{NR}_{12}$ , and  $\text{S}(\text{O})_m$ , and optionally comprises from one to three double bonds, and is optionally substituted with halo,  $\text{C}_1\text{-C}_4$  alkyl,  $-\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$ ,  $\text{NH}_2$ ,  $\text{NHCH}_3$ ,  $\text{N}(\text{CH}_3)_2$ ,  $\text{CF}_3$ , or  $\text{OCF}_3$ , with the proviso that said ring does not contain any  $-\text{S-S}-$ ,  $-\text{S-O}-$ ,  $-\text{N-S}-$ , or  $-\text{O-O}-$  bonds, and does not comprise more than two oxygen or  $\text{S}(\text{O})_m$  heterologous members;

$\text{R}_1$  is  $\text{C}(\text{O})\text{H}$ ,  $\text{C}(\text{O})(\text{C}_1\text{-C}_6 \text{ hydrocarbyl})$ ,  $\text{C}(\text{O})(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$ ,  $\text{C}(\text{O})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$ ,  $\text{C}(\text{O})(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$ ,  $-\text{C}(\text{O})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$ ,  $\text{C}_1\text{-C}_6 \text{ hydrocarbyl}$ ,  $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl}$ ,  $\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl}$ ,  $-(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$ ,  $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene}(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$ ,  $-(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$ ,  $-(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$ , or  $-\text{O-aryl}$ , or  $-\text{O}(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})\text{-aryl}$ ; wherein said aryl,  $\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl}$ ,  $\text{C}_1\text{-C}_6 \text{ hydrocarbyl}$ ,  $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl}$ ,  $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene}$ , and  $\text{C}_1\text{-C}_6 \text{ hydrocarbylene}$  groups may each independently be optionally substituted with from one to six

fluoro and may each independently be optionally substituted with one or two substituents  $R_8$  independently selected from the group consisting of  $C_1$ - $C_4$  hydrocarbyl,  $-C_3$ - $C_8$  cyclohydrocarbyl, hydroxy, chloro, bromo, iodo,  $CF_3$ ,  $-O$ -( $C_1$ - $C_6$  hydrocarbyl),  $-O$ -( $C_3$ - $C_5$  cyclohydrocarbyl),  $-O$ -CO-( $C_1$ - $C_4$  hydrocarbyl),  $-O$ -CO-NH( $C_1$ - $C_4$  hydrocarbyl),  $-O$ -CO-N( $R_{24}$ )( $R_{25}$ ),  $-N$ ( $R_{24}$ )( $R_{25}$ ),  $-S$ ( $C_1$ - $C_4$  hydrocarbyl),  $-S$ ( $C_3$ - $C_5$  cyclohydrocarbyl)  $-N$ ( $C_1$ - $C_4$  hydrocarbyl)CO( $C_1$ - $C_4$  hydrocarbyl),  $-NH$ CO( $C_1$ - $C_4$  hydrocarbyl),  $-COO$ ( $C_1$ - $C_4$  hydrocarbyl),  $-CONH$ ( $C_1$ - $C_4$  hydrocarbyl),  $-CONC_1$ - $C_4$  hydrocarbyl)( $C_1$ - $C_2$  hydrocarbyl),  $CN$ ,  $NO_2$ ,  $-OSO_2$ ( $C_1$ - $C_4$  hydrocarbyl),  $S^+$ ( $C_1$ - $C_6$  hydrocarbyl)( $C_1$ - $C_2$  hydrocarbyl),  $-SO$ ( $C_1$ - $C_4$  hydrocarbyl) and  $-SO_2$ ( $C_1$ - $C_4$  hydrocarbyl); and wherein the  $C_1$ - $C_6$  hydrocarbyl,  $C_1$ - $C_6$  hydrocarbylene,  $C_3$ - $C_8$  cyclohydrocarbyl,  $C_3$ - $C_8$  cyclohydrocarbylene, and  $C_3$ - $C_8$  heterocyclohydrocarbyl moieties of  $R_1$  may optionally independently contain from one to three double or triple bonds; and wherein the  $C_1$ - $C_4$  hydrocarbyl moieties and  $C_1$ - $C_6$  hydrocarbyl moieties of  $R_8$  can optionally independently be substituted with hydroxy, amino,  $C_1$ - $C_4$  alkyl, aryl,  $-CH_2$ -aryl,  $C_3$ - $C_5$  cycloalkyl, or  $-O$ -( $C_1$ - $C_4$  alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocyclohydrocarbyl group of  $R_1$  contains from one to three heteromoieties selected from oxygen,  $S(O)_m$ , nitrogen, and  $NR_{12}$ ;

$R_2$  is hydrogen,  $C_1$ - $C_{12}$  hydrocarbyl,  $C_3$ - $C_8$  cyclohydrocarbyl,  $C_4$ - $C_8$  heterocyclohydrocarbyl,  $-(C_1$ - $C_6$  hydrocarbylene)( $C_3$ - $C_8$  cyclohydrocarbyl),  $-(C_3$ - $C_8$  cyclohydrocarbylene)( $C_3$ - $C_8$  cyclohydrocarbyl),  $-(C_1$ - $C_6$  hydrocarbylene)( $C_4$ - $C_8$  heterocyclohydrocarbyl),  $-(C_3$ - $C_6$  cyclohydrocarbylene)( $C_4$ - $C_8$  heterocyclohydrocarbyl), aryl,  $-(C_1$ - $C_6$  hydrocarbylene)aryl, or  $-(C_3$ - $C_8$  cyclohydrocarbylene)(aryl); wherein each of the foregoing  $R_2$  groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and  $C_1$ - $C_6$  alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo,  $C_1$ - $C_6$  alkoxy,  $-OH$ ,  $-O$ -CO-( $C_1$ - $C_6$  alkyl),  $-O$ -CO-N( $C_1$ - $C_4$  alkyl)( $C_1$ - $C_2$  alkyl),  $-S$ ( $C_1$ - $C_6$  alkyl),  $-S(O)$ ( $C_1$ - $C_6$  alkyl),  $-S(O)_2$ ( $C_1$ - $C_6$  alkyl),  $S^+$ ( $C_1$ - $C_6$  alkyl)( $C_1$ - $C_2$  alkyl)I',  $CN$ , and  $NO_2$ ; and wherein the  $C_1$ - $C_{12}$  hydrocarbyl,  $-(C_1$ - $C_6$  hydrocarbylene), and cyclohydrocarbyl groups of 5 - 8 carbon atoms, cyclohydrocarbylene groups of 5 to 8 carbon atoms and heterocyclohydrocarbyl groups of 5 to 8 atoms of  $R_2$  may optionally independently contain from one to three double or triple bonds; and wherein each heterocyclohydrocarbyl group of  $R_2$  contains from one to three heteromoieties selected from oxygen,  $S(O)_m$ , nitrogen, and  $NR_{12}$ ;

or when  $R_1$  and  $R_2$  are as in  $-NHCHR_1R_2$ ,  $-OCHR_1R_2$ ,  $-SCHR_1R_2$ ,  $-CHR_1R_2$  or  $-NR_1R_2$ ,  $R_1$  and  $R_2$  of B may form a saturated 5- to 8-membered ring which may optionally contain one

or

two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen,  $S(O)_m$ , nitrogen or  $NR_{12}$ ; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy,  $C_1$ - $C_4$  alkyl, fluoro, chloro, bromo, iodo,  $CF_3$ ,  $-O-(C_1-C_4 \text{ alkyl})$ ,  $-O-CO-(C_1-C_4 \text{ alkyl})$ ,  $-O-CO-NH(C_1-C_4 \text{ alkyl})$ ,  $-O-CO-N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$ ,  $-NH(C_1-C_4 \text{ alkyl})$ ,  $-N(C_1-C_2 \text{ alkyl})(C_1-C_4 \text{ alkyl})$ ,  $-S(C_1-C_4 \text{ alkyl})$ ,  $-N(C_1-C_4 \text{ alkyl})CO(C_1-C_4 \text{ alkyl})$ ,  $-NHCO(C_1-C_4 \text{ alkyl})$ ,  $-COO(C_1-C_4 \text{ alkyl})$ ,  $-CONH(C_1-C_4 \text{ alkyl})$ ,  $-CON(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$ ,  $CN$ ,  $NO_2$ ,  $-OSO_2(C_1-C_4 \text{ alkyl})$ ,  $-SO(C_1-C_4 \text{ alkyl})$ , and  $-SO(C_1-C_4 \text{ alkyl})$ , wherein one of said one to three substituents can further be selected from phenyl;

$R_3$  is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy,  $OCF_3$ ,  $NH_2$ ,  $NH(C_1-C_2 \text{ alkyl})$ ,  $N(CH_3)_2$ ,  $-NHCOCF_3$ ,  $-NHCH_2CF_3$ ,  $S(O)_m(C_1-C_4 \text{ alkyl})$ ,  $CONH_2$ ,  $-CONHCH_3$ ,  $CON(CH_3)_2$ ,  $-CF_3$ , or  $CH_2OCH_3$ ;

$R_4$  is hydrogen,  $C_1$ - $C_4$  hydrocarbyl,  $C_3$ - $C_5$  cycloalkyl,  $-(C_1-C_4 \text{ hydrocarbylene})(C_3-C_5 \text{ cycloalkyl})$ ,  $-(C_3-C_5 \text{ cycloalkylene})(C_3-C_6 \text{ cycloalkyl})$ , cyano, fluoro, chloro, bromo, iodo,  $-OR_{24}$ ,  $C_1$ - $C_6$  alkoxy,  $-O-$  cycloalkyl,  $-O-(C_1-C_4 \text{ hydrocarbylene})(C_3-C_5 \text{ cycloalkyl})$ ,  $-O-(C_3-C_5 \text{ cycloalkylene})(C_3-C_5 \text{ cycloalkyl})$ ,  $-CH_2SC(S)O(C_1-C_4 \text{ alkyl})$ ,  $CH_2OCF_3$ ,  $CF_3$ , amino, nitro,  $-NR_{24}R_{25}$ ,  $-(C_1-C_4 \text{ hydrocarbylene})-OR_{24}$ ,  $-(C_1-C_4 \text{ hydrocarbylene})Cl$ ,  $-(C_1-C_4 \text{ hydrocarbylene})NR_{24}R_{25}$ ,  $-NHCOR_{24}$ ,  $-NHCONR_{24}R_{25}$ ,  $-CH=NOR_{24}$ ,  $-NHNr_{24}R_{25}$ ,  $-S(O)_mR_{24}$ ,  $-C(O)R_{24}$ ,  $-OC(O)R_{24}$ ,  $-C(O)CN$ ,  $-C(O)NR_{24}R_{25}$ ,  $-C(O)NHNr_{24}R_{25}$ , and  $-COOR_{24}$ , wherein the hydrocarbyl and hydrocarbylene groups of  $R_4$  may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents  $R_{10}$  independently selected from hydroxy, amino,  $-NHCOCCH_3$ ,  $-NHCOCCH_2Cl$ ,  $-NH(C_1-C_2 \text{ alkyl})$ ,  $-N(C_1-C_2 \text{ alkyl})(C_1-C_2 \text{ alkyl})$ ,  $-COO(C_1-C_4 \text{ alkyl})$ ,  $-COOH$ ,  $-CO(C_1-C_4 \text{ alkyl})$ ,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_3$  thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

$R_5$  is aryl or heteroaryl and is substituted with from one to four substituents  $R_{27}$  independently selected from halo,  $C_1$ - $C_{10}$  hydrocarbyl,  $-(C_1-C_4 \text{ hydrocarbylene})(C_3-C_8 \text{ cycloalkyl})$ ,  $-(C_1-C_4 \text{ hydrocarbylene})(C_4-C_8 \text{ heterocycloalkyl})$ ,  $-(C_3-C_8 \text{ cycloalkyl})$ ,  $-(C_4-C_8 \text{ heterocycloalkyl})$ ,  $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$ ,  $-(C_3-C_8 \text{ cycloalkylene})(C_4-C_8 \text{ heterocycloalkyl})$ ,  $C_1$ - $C_4$  haloalkyl,  $C_1$ - $C_4$  haloalkoxy, nitro, cyano,  $-NR_{24}R_{25}$ ,  $-NR_{24}COR_{25}$ ,  $-NR_{24}CO_2R_{26}$ ,  $-COR_{24}$ ,  $-OR_{25}$ ,  $-CONR_{24}R_{25}$ ,  $-CON(OR_{22})R_{23}$ ,  $-CO_2R_{26}$ ,  $-C=N(OR_{22})R_{23}$ , and  $-S(O)_mR_{23}$ ; wherein said  $C_1$ - $C_{10}$  alkyl,  $C_3$ - $C_8$  cycloalkyl,  $(C_1-C_4 \text{ hydrocarbylene})$ ,  $(C_3-C_8 \text{ cycloalkyl})$ ,  $(C_3-C_8 \text{ cycloalkylene})$ , and  $(C_4-C_8 \text{ heterocycloalkyl})$  groups can be optionally substituted with from one to three substituents independently selected from  $C_1$ - $C_4$  alkyl,  $C_3$ - $C_8$

cycloalkyl, (C<sub>1</sub>-C<sub>4</sub> hydrocarbylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), C<sub>1</sub>-C<sub>4</sub> haloalkyl, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, nitro, halo, cyano, -NR<sub>24</sub>R<sub>25</sub>, -NR<sub>24</sub>COR<sub>25</sub>, NR<sub>24</sub>CO<sub>2</sub>R<sub>26</sub>, -COR<sub>24</sub>, -OR<sub>25</sub>, -CONR<sub>24</sub>R<sub>25</sub>, CO<sub>2</sub>R<sub>26</sub>, -CO(NOR<sub>22</sub>)R<sub>25</sub>, and -S(O)<sub>m</sub>R<sub>23</sub>; and wherein two adjacent substituents of the R<sub>5</sub> group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R<sub>5</sub>, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)<sub>m</sub>, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), C<sub>1</sub>-C<sub>4</sub> haloalkyl, nitro, halo, cyano -NR<sub>24</sub>R<sub>25</sub>, NR<sub>24</sub>COR<sub>25</sub>, NR<sub>24</sub>CO<sub>2</sub>R<sub>26</sub>, -COR<sub>24</sub>, -OR<sub>25</sub>, -CONR<sub>24</sub>R<sub>25</sub>, CO<sub>2</sub>R<sub>26</sub>, -CO(NOR<sub>26</sub>)R<sub>25</sub>, or -S(O)<sub>m</sub>R<sub>23</sub>; wherein one of said one to four optional substituents R<sub>27</sub>, can further be selected from -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -SO<sub>2</sub>NH(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), SO<sub>2</sub>NH(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -SO<sub>2</sub>NH(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl), -SO<sub>2</sub>NH<sub>2</sub>, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), -NHSO<sub>2</sub>(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), and -NHSO<sub>2</sub>(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl); and wherein the hydrocarbyl, and hydrocarbylene groups of R<sub>5</sub> may independently optionally contain one double or triple bond;

R<sub>6</sub> is hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>6</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), or -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

or R<sub>6</sub> and R<sub>4</sub> can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous ring members selected from O, SO<sub>m</sub>, N, and NR<sub>12</sub>, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C<sub>1</sub>-C<sub>4</sub> hydrocarbyl or C<sub>3</sub>-C<sub>6</sub> cycloalkyl, wherein said C<sub>1</sub>-C<sub>4</sub> hydrocarbyl substituent may optionally contain one double or triple bond;

R<sub>11</sub> is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R<sub>12</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sub>22</sub> is independently at each occurrence selected from hydrogen, C<sub>1</sub>-C<sub>14</sub> alkyl, C<sub>1</sub>-C<sub>14</sub> haloalkyl, C<sub>3</sub>-C<sub>6</sub> alkenyl, C<sub>3</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, (C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), and (C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl);

R<sub>23</sub> is independently at each occurrence selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>2</sub>-C<sub>8</sub> alkoxyalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), aryl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

R<sub>24</sub> and R<sub>25</sub> are independently at each occurrence selected from hydrogen, -C<sub>1</sub>-C<sub>4</sub> alkyl,

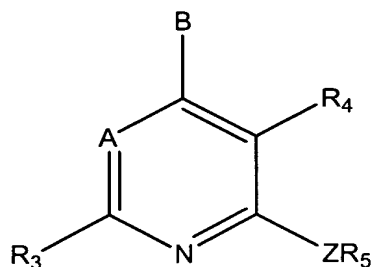
C<sub>1</sub>-C<sub>4</sub> haloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)OH, -(C<sub>1</sub>-C<sub>4</sub> alkylene)-O-(C<sub>1</sub>-C<sub>4</sub> alkyl), -(C<sub>1</sub>-C<sub>4</sub> alkylene)-O-(C<sub>3</sub>-C<sub>5</sub> cycloalkyl), C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -C<sub>4</sub>-C<sub>8</sub> heterocyclohydrocarbyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>4</sub>-C<sub>8</sub> heterocyclohydrocarbyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>4</sub>-C<sub>8</sub> heterocyclohydrocarbyl), aryl, and -(C<sub>1</sub>-C<sub>4</sub> alkylene)(aryl), wherein the -C<sub>4</sub>-C<sub>8</sub> heterocyclohydrocarbyl groups can each independently optionally be substituted with aryl, CH<sub>2</sub>-aryl, or C<sub>1</sub>-C<sub>4</sub> alkyl, and can optionally contain one or two double or triple bonds; or, when R<sub>24</sub> and R<sub>25</sub> are as NR<sub>24</sub>R<sub>25</sub>, -C(O)NR<sub>24</sub>R<sub>25</sub>, -(C<sub>1</sub>-C<sub>4</sub> alkylene)NR<sub>24</sub>R<sub>25</sub>, or -NHCONR<sub>24</sub>R<sub>25</sub>, then NR<sub>24</sub>R<sub>25</sub> may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from S(O)<sub>m</sub>, oxygen, nitrogen, and NR<sub>12</sub>, and optionally containing from one to three double bonds;

R<sub>26</sub> is independently at each occurrence selected from C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> haloalkyl, C<sub>3</sub>-C<sub>8</sub> cycloalkyl, -(C<sub>1</sub>-C<sub>4</sub> alkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), -(C<sub>3</sub>-C<sub>8</sub> cycloalkylene)(C<sub>3</sub>-C<sub>8</sub> cycloalkyl), aryl, and -(C<sub>1</sub>-C<sub>4</sub> alkylene)(aryl); and

wherein each m is independently zero, one, or two,

with the proviso that heterocyclohydrocarbylene groups of the compound of formula I, do not comprise any -S-S-, -S-O-, -N-S-, or -O-O- bonds, and do not comprise more than two oxygen or S(O)<sub>m</sub> heterologous members.

Claim 2 (Twice Amended). A compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is N;

B is -NR<sub>1</sub>R<sub>2</sub>, -CR<sub>1</sub>R<sub>2</sub>R<sub>11</sub>, -C(=CR<sub>2</sub>R<sub>12</sub>)R<sub>1</sub>, -NHCHR<sub>1</sub>R<sub>2</sub>, -OCHR<sub>1</sub>R<sub>2</sub>, -SCHR<sub>1</sub>R<sub>2</sub>, -CHR<sub>2</sub>OR<sub>12</sub>, -CHR<sub>2</sub>SR<sub>12</sub>, -C(S)R<sub>2</sub> or -C(O)R<sub>2</sub>;

Z is -NH, O, S, N(C<sub>1</sub>-C<sub>2</sub> alkyl) or C(R<sub>13</sub>R<sub>14</sub>) wherein R<sub>13</sub> and R<sub>14</sub> are each independently, hydrogen, trifluoromethyl or methyl or one of R<sub>13</sub> and R<sub>14</sub> is cyano and the other is hydrogen or methyl;

R<sub>1</sub> is C<sub>1</sub>-C<sub>6</sub> hydrocarbyl which may optionally be substituted with one or two substituents

R<sub>8</sub> independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkoxy, -O-CO-(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -O-CO-NH(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -O-CO-N(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl)(C<sub>1</sub>-C<sub>2</sub> hydrocarbyl), -NH(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -N(C<sub>1</sub>-C<sub>2</sub> alkyl)(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -S(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(C<sub>1</sub>-C<sub>4</sub>)CO(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -NHCO(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -COO(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl)hydrocarbyl, -CONH(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -CON(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl)(C<sub>1</sub>-C<sub>2</sub> alkyl), CN, NO<sub>2</sub>, -SO(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl) and -SO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), and wherein said C<sub>1</sub>-C<sub>6</sub> hydrocarbyl and the (C<sub>1</sub>-C<sub>4</sub>)hydrocarbyl moieties in the foregoing R<sub>1</sub> groups may optionally contain one carbon-carbon double or triple bond;

R<sub>2</sub> is C<sub>1</sub>-C<sub>12</sub> hydrocarbyl, aryl or -(C<sub>1</sub>-C<sub>4</sub> hydrocarbylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C<sub>1</sub>-C<sub>6</sub> alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C<sub>1</sub>-C<sub>6</sub> alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N-R<sub>9</sub> wherein R<sub>9</sub> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; and wherein each of the foregoing R<sub>2</sub> groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C<sub>1</sub>-C<sub>4</sub> alkyl, or with one substituent selected from bromo, iodo, C<sub>1</sub>-C<sub>6</sub> alkoxy, -O-CO-(C<sub>1</sub>-C<sub>6</sub> alkyl), -O-CO-N(C<sub>1</sub>-C<sub>4</sub> alkyl)(C<sub>1</sub>-C<sub>2</sub> alkyl), -S(C<sub>1</sub>-C<sub>6</sub> alkyl), CN, NO<sub>2</sub>, -SO(C<sub>1</sub>-C<sub>4</sub> alkyl), and -SO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub> alkyl), and wherein said C<sub>1</sub>-C<sub>12</sub> hydrocarbyl and the C<sub>1</sub>-C<sub>4</sub> hydrocarbylene moiety of said -(C<sub>1</sub>-C<sub>4</sub> hydrocarbylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR<sub>1</sub>R<sub>2</sub> or -CR<sub>1</sub>R<sub>2</sub>R<sub>11</sub> may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R<sub>3</sub> is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF<sub>3</sub>, methylthio, methylsulfonyl, CH<sub>2</sub>OH, or CH<sub>2</sub>OCH<sub>3</sub>;

R<sub>4</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> hydrocarbyl, fluoro, chloro, bromo, iodo, C<sub>1</sub>-C<sub>4</sub> alkoxy, trifluoromethoxy, -CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OCH<sub>2</sub>CH<sub>3</sub>, -CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, -CH<sub>2</sub>OF<sub>3</sub>, CF<sub>3</sub>, amino, nitro, -NH(C<sub>1</sub>-C<sub>4</sub> alkyl), -N(CH<sub>3</sub>)<sub>2</sub>, -NHCOCH<sub>3</sub>, -NHCONHCH<sub>3</sub>, -SO<sub>n</sub>(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C<sub>1</sub>-C<sub>4</sub> hydrocarbyl), -CHO, cyano or -COO(C<sub>1</sub>-C<sub>4</sub> alkyl) wherein said C<sub>1</sub>-C<sub>4</sub> hydrocarbyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH<sub>3</sub>, -NH(C<sub>1</sub>-C<sub>2</sub> alkyl), -N(C<sub>1</sub>-C<sub>2</sub> alkyl)<sub>2</sub>, -COO(C<sub>1</sub>-C<sub>4</sub> alkyl), -CO(C<sub>1</sub>-C<sub>4</sub> alkyl), C<sub>1</sub>-C<sub>3</sub> alkoxy, C<sub>1</sub>-C<sub>3</sub> thioalkyl, fluoro, chloro, cyano and nitro;

R<sub>5</sub> is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl,



furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups  $R_5$  is substituted with from one to three substituents independently selected from fluoro, chloro,  $C_1$ - $C_6$  alkyl, and  $C_1$ - $C_6$  alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino,  $-(C_1-C_6 \text{ alkyl})O(C_1-C_6 \text{ alkyl})$ ,  $-NHCH_3$ ,  $-N(CH_3)_2$ ,  $-COOH$ ,  $-COO(C_1-C_4 \text{ alkyl})$ ,  $-CO(C_1-C_4 \text{ alkyl})$ ,  $-SO_2NH(C_1-C_4 \text{ alkyl})$ ,  $-SO_2N(C_1-C_4 \text{ alkyl})(C_1-C_2 \text{ alkyl})$ ,  $-SO_2NH_2$ ,  $-NHSO_2(C_1-C_4 \text{ alkyl})$ ,  $-S(C_1-C_6 \text{ alkyl})$  and  $[-SO_2(C_1-C_6 \text{ alkyl})] -SO_2(C_1-C_6 \text{ alkyl})$ , and wherein the  $C_1$ - $C_4$  alkyl and  $C_1$ - $C_6$  alkyl moieties of the foregoing  $R_5$  groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

$R_{11}$  is hydrogen, hydroxy, fluoro, or methoxy;

$R_{12}$  is hydrogen or  $C_1$ - $C_4$  alkyl; and

or a pharmaceutically acceptable salt of such compound.

Claim 12 (Amended). A compound according to claim 1, wherein said compound is selected from the group consisting of:

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-diethyl-amine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-propyl-amine;

butyl-[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-amine;

4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridine;

butyl-[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-amine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenylsulfanyl)-pyridin-4-yl]-ethyl-propyl-amine;

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-ethyl-propyl-amine;

N4-(1-ethyl-propyl)-6-methyl-3-nitro-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,4-diamine;

3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-ethyl-(2,2,2-trifluoro-ethyl)-amine;

N4-(1-ethyl-propyl)-6-methyl-N2-(2,4,6-trimethyl-phenyl)-pyridine-2,3,4-triamine;

(N-(1-ethyl-propyl)-2-methyl-5-nitro-N'-(2,4,6-trimethyl-pyridin-3-yl)-pyrimidine-4,6-diamine;

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-diethyl-amine;

(1-ethyl-propyl)-[5-methyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo [4,5-b]pyridin-7-yl]-amine;

[2,5-dimethyl-3-(2,4,6-trimethyl-phenyl)-3H-imidazo[4,5-b]pyridin-4-yl]-(1-ethyl-propyl)-amine; [or]

[4-(1-ethyl-propoxy)-3,6-dimethyl-pyridin-2-yl]-(2,4,6-trimethylphenyl)-amine;

[4-(1-ethyl-propoxy)-3,6-dimethyl-2-(2,4,6-trimethylphenoxy)-pyridine;

[3,6-dimethyl-2-(2,4,6-trimethyl-phenoxy)-pyridin-4-yl]-(1-ethyl-propyl)-amine; and

[2-(4-chloro-2,6-dimethyl-phenoxy)-3,6-dimethyl-pyridin-4-yl]-(1-ethyl-propyl)-amine

or pharmaceutically acceptable salt of one of the above compounds.

Claim 13 (Twice Amended). A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF or (b) a disorder or condition selected from inflammatory disorders, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception [such as fibromyalgia]; mood disorders, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases, gastrointestinal diseases; eating disorder; hemorrhagic stress; chemical dependencies or addictions; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage, [including cerebral ischemia;] epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

Claim 14 (Twice Amended). A pharmaceutical composition according to claim 13 for the treatment of a disorder selected from inflammatory disorders; pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception; mood disorders [such as depression,, and postpartum depression]; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; gastrointestinal diseases; eating disorders; chemical dependencies and addictions; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal[, including a human].

Claim 29 (Amended). A compound as claimed in claim 1 wherein [R24 and R25]  
R<sub>24</sub> and R<sub>25</sub> are selected from -CF<sub>3</sub>, -CHF<sub>2</sub>, CF<sub>2</sub>CF<sub>3</sub>, and CH<sub>2</sub>CF<sub>3</sub>,

Claim 32 (Amended). A pharmaceutical composition as claimed in claim 14 for treatment of depression, selected from the group consisting of major depression, single episode depression, recurrent depression, and child abuse induced depression.

Claim 36 (Amended). A pharmaceutical composition as claimed in claim 14 for treatment of [stress induced] immune dysfunctions induced by stress selected from the group consisting of [including] porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs.

Claim 40 (Amended). A pharmaceutical composition as claimed in claim 14 for treatment of social phobia, agoraphobia, or specific phobias.